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(54) Title: ANTI–TUMOR SYNERGETIC COMPOSITION

(57) Abstract

There are provided the combined use of 4–demethoxy–3'–deamino–3'–aziridinyl–4'–methansulfonyl daunorubicin or 4–demethoxy–N,N–bis(2–chloroethyl)–4'–methansulfonyl daunorubicin and an anti–neoplastic anti–mitotic compound and/or a platinum derivative in the treatment of tumors, as well as in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis.

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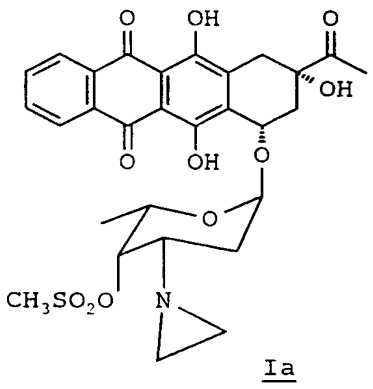
Anti-tumor Synergetic Composition

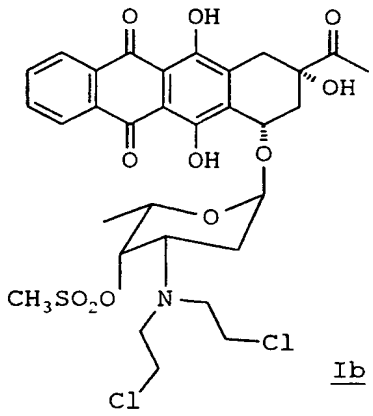
The present invention relates in general to the field of cancer treatment and, more particularly, provides an anti-tumor composition comprising an alkylating anthracycline and an anti-mitotic compound and/or a platinum derivative, having a synergistic or additive anti-neoplastic effect.

The present invention provides, in a first aspect, a pharmaceutical composition for use in anti-neoplastic therapy in mammals, including humans, comprising

- an anthracycline of formula Ia or Ib :



Ia



Ib

- an anti-neoplastic anti-mitotic compound and/or a platinum derivative, and a pharmaceutically acceptable carrier or excipient.

The chemical names of the anthracyclines of formula Ia and Ib are 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (Ia) and 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin (Ib). These anthracyclines were described in Anticancer Drug Design (1995), vol. 10, 641-653, and claimed respectively in US-A-5,532,218 and US-A-5,496,800. Both compounds intercalate into DNA via the chromophore and alkylate guanine at N7 position in DNA minor groove via their reactive moiety on

position 3' of the amino sugar. Compounds Ia and Ib are able to circumvent the resistance to all major classes of cytotoxics, indicating that the compounds represent a new class of cytotoxic anti-tumor drugs.

Anti-mitotic and platinum derivatives anti-neoplastic agents are described in various scientific publications. The main representatives of the anti-mitotic class are: Paclitaxel, Docetaxel, Vinblastine, Vincristine, Vindesine and Vinorelbine; see for example the review: Cancer, Principles and Practice of Oncology, Lippincott-Raven Ed. (1997), 467-483. Platinum derivatives used in clinical practice are: CisPlatin, Carboplatin, Oxaliplatin, Nedaplatin and Lobaplatin; see review Cancer, Principles and Practice of Oncology, Lippincott-Raven Ed. (1997), 418-432.

4-Demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin is the preferred compound to be used in the present invention, more preferably in combination with oxaliplatin docetaxel or paclitaxel. The present invention also provides a product comprising an anthracycline of formula Ia or Ib as defined above and an anti-neoplastic anti-mitotic compound and/or a platinum derivative, as combined preparation for simultaneous, separate or sequential use in antitumor therapy.

A further aspect of the present invention is to provide a method of treating a mammal including humans, suffering from a neoplastic disease state comprising administering to said mammal an anthracycline of formula Ia or Ib as defined above and an anti-neoplastic anti-mitotic compound and/or a platinum derivative, in amounts effective to produce a synergetic anti-neoplastic effect.

The present invention also provides a method for lowering the side effects caused by anti-neoplastic therapy with an anti-neoplastic agent in mammals, including humans, in need

thereof, the method comprising administering to said mammal a combination preparation comprising an anti-neoplastic anti-mitotic compound and/or a platinum derivative as defined above and an anthracycline of formula Ia or Ib, as defined above, in amounts effective to produce a synergistic anti-neoplastic effect.

By the term "a synergistic anti-neoplastic effect" as used herein is meant the inhibition of the growth tumor, preferably the complete regression of the tumor, administering an effective amount of the combination of an anthracycline of formula Ia or Ib as defined above and an anti-mitotic compound and/or a platinum derivative to mammals, including human.

By the term "administered " or "administering" as used herein is meant parenteral and /or oral administration. By "parenteral" is meant intravenous, subcutaneous and intramuscolar administration. In the method of the subject invention, the anthracycline may be administered simultaneously with the compound with anti-mitotic activity, and/or a platinum derivative, or the compounds may be administered sequentially, in either order. It will be appreciated that the actual preferred method and order of administration will vary according to, inter alia, the particular formulation of the anthracycline of formula Ia or Ib being utilized, the particular formulation of the anti-mitotic compound, such as one of taxane analog class and of the platinum derivative being utilized, the particular tumor model being treated, and the particular host being treated .

In the method of the subject invention, for the administration of the anthracycline of formula Ia or Ib, the course of therapy generally employed is from about 0.1 to about 200 mg/m^2 of body surface area. More preferably,

the course therapy employed is from about 1 to about 50 mg/m^2 of body surface area.

In the method of the subject invention, for the administration of the anti-mitotic compounds the course of therapy generally employed is from about 1 to about 1000 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 10 to about 500 mg/m^2 of body surface area.

In the method of the subject invention, for the administration of the platinum derivative the course of therapy generally employed is from about 1 to about 1000 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 100 to about 500 mg/m^2 of body surface area. The anti-neoplastic therapy of the present invention is in particular suitable for treating breast, ovary, lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors in mammals, including humans.

In a further aspect, the present invention is directed to the preparation of a pharmaceutical composition containing an effective amount of an anthracycline of formula Ia or Ib as defined above and an anti-neoplastic anti-mitotic compound and/or a platinum derivative in the prevention or treatment of metastasis or for the treatment of tumors by angiogenesis inhibition, as well as to the use of an anthracycline of formula Ia or Ib as defined above and an anti-neoplastic anti-mitotic compound and/or a platinum derivative for the treatment of tumors by angiogenesis inhibition or for the treatment or prevention of metastasis.

As stated above, the effect of an anthracycline of formula Ia or Ib and an anti-neoplastic anti-mitotic compounds, such as taxane derivatives, and/or a platinum derivative is significantly increased without a parallel increased

toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline and/or of the anti-mitotic compound and/or of the platinum derivative and thus yields the most effective and less toxic treatment for tumors. The superadditive actions of the combination preparation of the present invention are shown for instance by the following *in vivo* tests, which are intended to illustrate but not to limit the present invention.

Table 1 shows the antileukemic activity on disseminated L1210 murine leukemia obtained combining Ia with oxaliplatinum. At the dose of 8 mg/kg of oxaliplatinum alone (day +3) and at the dose of 1 mg/kg of Ia alone (day +1,2) were associated, without toxicity, with increase in life span (ILS%) values of 83 for both. Combining oxaliplatinum and Ia at the same doses with the same schedule an increase antitumor activity with ILS% value of 125 was observed, indicating a synergistic effect of the combination.

For these experiments Ia was solubilized in [Cremophor® /EtOH= 6.5:3.5]/[normal saline]=20/80 v/v, while oxaliplatinum was solubilized in saline solution.

Table 1: Antileukemic activity against disseminated L1210[1] murine leukemia of Ia in combination with Oxaliplatinum

Compound	Treatment schedule	Dose[2] (mg/kg/day)	ILS%[3]	Tox[4]
Ia	iv +1,2	1	83	0/10
Oxaliplatinum	ip +3	8	83	0/10
Ia + Oxaliplatinum	iv+1,2 ip +3	1 + 8	125	0/10

1) L1210 leukemia cells (10^5/mouse) are injected iv on day 0.

2) Treatment is given starting on day 1 after tumor transplantation (day 0).

3) Increase in life span: [(median survival time of treated mice/median survival time of controls)x 100]-100

4) Number of toxic deaths/number of mice.

Table 2 shows the antitumor effect on subcutaneous implanted A549 human lung carcinoma obtained combining Ia with CisPlatin. At the doses of 3 mg/kg of CisPlatin alone (q4dx2) and at the dose of 1.5 mg/kg of Ia alone (q4dx3) were associated, without toxicity, with T.I.% values of 16 and 48, respectively. Combining CisPlatin and Ia, a significant increase in tumor growth delay was observed indicating a therapeutic advantage of the combination in comparison with the administration of the drug alone.

Table 2: Antitumor activity on A549 human lung carcinoma[1] of Ia in combination with CisPlatin

Compound	Treatment[2] schedule	Dose (mg/kg /day)	T.I. %[3]	Tox[4]	N° of Tumor-Free Survivors	T-C[5] N°of days	Body weight Reduction % (day)
Ia	iv q4dx3	1.5	48	0/9	0/9	5	9(14)
CisPlatin	iv q4dx2[6]	3	16	0/9	0/9	0	2(18)
Ia + CisPlatin	iv q4dx3 + iv q4dx2[6]	1.5 + 22	67	0/9	0/9	12	19(20)

1)Tumor fragments are implanted s.c.
2)Treatment is given starting when the tumor is palpable.
3)Tumor inhibiton.
4)Number of toxic deaths/number of mice.
5)Tumor growth delay; T, median time to reach a tumor size of 1 g treated nude mice; C, median time to reach a tumor size of 1 g in control nude mice.
6)Treatment with CisPlatin started two days after treatment with Ia

Table 3 shows the antitumor effect on subcutaneus implanted A549 human lung carcinoma obtained combining Ia with

paclitaxel. At the doses of 22 and 33 mg/kg of paclitaxel alone(days +9,13,17)and at the dose of 2 mg/kg of Ia alone (days +7,11,15)were associated, without toxicity, with T.I.% values of 69,90 and 93, respectively. Combining paclitaxel and Ia, a significant increase in tumour growth delay was observed indicating a therapeutic advantage of the combination in comparison with the administration of the drug alone.

Table 3: Antitumor activity on A549 human lung carcinoma[1] of Ia in combination with paclitaxel

Compound	Treatment[2] schedule	Dose (mg/kg /day)	T.I. %[3]	Tox[4]	N° of Tumor-Free Survivors	T-C[5] N°of days	Body weight Reduction % (day)
Ia	iv+7,11,15	2	69	0/8	0/8	9	11 (13)
Paclitaxel	iv+9,13,17	22	90	0/8	0/8	27	0
		33	93	0/8	0/8	29	0
Ia + Paclitaxel	iv 7,11,15 + iv 9,13,17	2 + 22	93	1/8	0/8	35	18 (15)
Ia+ Paclitaxel	iv 7,11,15 + iv 9,13,17	2 + 33	90	0/6	0/6	40	23 (22)

1) Tumor fragments are implanted s.c.
2) Treatment is given starting when the tumor is palpable.
3) Tumor inhibiton.
4) Number of toxic deaths/number of mice.
5) Tumor growth delay; T, median time to reach a tumor size of 1 g treated nude mice; C, median time to reach a tumor size of 1 g in control nude mice.

Table 4 shows the antitumor effect on subcutaneous implanted H207 human ovarian carcinoma obtained combining Ia with paclitaxel. At the doses of 22 and 33 mg/kg of paclitaxel alone (q4dx3)and at the dose of 1.5 mg/kg of Ia alone (q4dx3) were associated, without toxicity, with T.I.%

values of 100,80 and 86, respectively. Combining paclitaxel and Ia, a significant increase in tumor growth delay and the appearance of the tumor free survivors (1/7 and 4/7) was observed indicating a therapeutic advantage of the combination in comparison with the administration of the drug alone.

Table 4: Antitumor activity on H207 human ovarian carcinoma[1] of Ia in combination with paclitaxel

Compound	Treatment[2] Schedule	Dose (mg/kg /day)	T.I. %[3]	Tox[4]	N° of Tumor-Free Survivors	T-C[5] N°of days	Body weight Reduction % (day)
Ia	iv q4dx3	1.5	100	0/7	0/7	47	7 (15)
Paclitaxel	iv q4dx3[6]	22	80	0/7	0/7	9	0
		33	86	0/7	0/7	12	3(13)
Ia + Paclitaxel	iv q4dx3 + iv q4dx3[6]	1.5 + 22	100	0/7	1/7	>71	8 (20)
Ia+ Paclitaxel	iv q4dx3 + iv q4dx3[6]	1.5 + 33	100	0/7	4/7	>71	10 (16)

1)Tumor fragments are implanted s.c.
2) Treatment is given starting when the tumor is palpable.
3)Tumor inhibiton.
4) Number of toxic deaths/number of mice.
5) Tumor growth delay; T, median time to reach a tumor size of 1 g treated nude mice; C, median time to reach a tumor size of 1 g in control nude mice.
6)Treatment with paclitaxel started two days after treatment with Ia

Table 5 shows the antitumor effect on subcutaneous injected MX1 mammary carcinoma obtained combining Ia with docetaxel. At the doses of 5 and 10 mg/kg of docetaxel alone (q4dx3)and at the dose of 0.5 and 1 mg/kg of Ia alone (q4dx3) were associated, without toxicity, with T.I.% values of 60,99 and 46,94 respectively. Combining docetaxel and Ia, a significant increase in tumor growth delay and of

the tumor free survivors (3/8, 5/8 and 7/8) was observed indicating a therapeutic advantage of the combination in comparison with the administration of the drug alone.

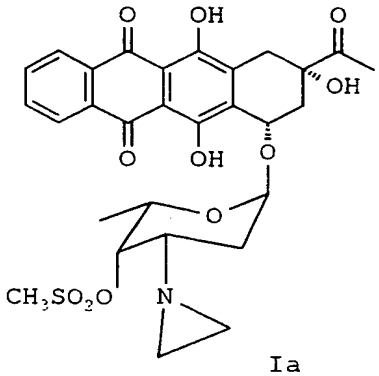
Table 5: Antitumor activity on MX1 mammary carcinoma[1] of Ia in combination with paclitaxel

Compound	Treatment[2] Schedule	Dose (mg/kg/ day)	T.I. %[3]	Tox[4]	N° of Tumor-Free Survivors	TGD[5] (1g) days	Body weight Reduction % (day)
Ia	iv 8,12,16	0.5	46	0/8	0/8	1	0
		1	94	0/7	1/7	2	5 (17)
Taxotere	iv 10,14,18	5	60	0/8	0/8	1	0
		10	99	0/8	2/8	42	8 (25)
Ia	iv 8,12,16	0.5 + 5	95	0/8	3/8	2	6 (17)
Taxotere	iv 10,14,18	0.5+ 10	96	0/8	5/8	>78	11 (17)
		1+5	98	0/8	7/8	>78	10(17)
		1 + 10	98	3/8	5/8	>78	15 (18)

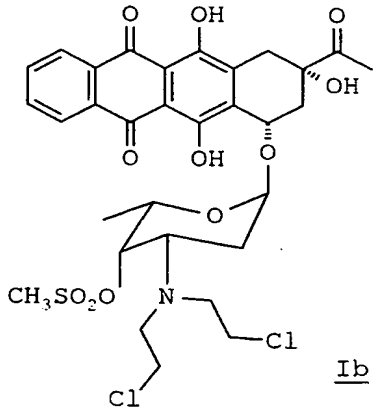
1) Tumor fragments were injected s.c.
2) Treatment is given starting when the tumor is palpable.
3) Tumor inhibiton.
4) Number of toxic deaths/number of mice.
5) TGD : Tumor growth delay treated - Tumor growth delay control

Claims

1. Products containing an anthracycline of formula Ia or Ib:



Ia



Ib

and an anti-neoplastic anti-mitotic compound and/or a platinum derivative as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

2. Products according to claim 1 wherein the anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin.

3. Products according to claim 1 or 2 wherein the anti-mitotic compound is paclitaxel or docetaxel.

4. Products according to claim 1 or 2 wherein the platinum derivative is oxaliplatin.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient, an anthracycline of formula Ia or Ib as defined in claim 1 and
an anti-neoplastic anti-mitotic compound and/or a platinum derivative.

6. A composition according to claim 5 wherein the anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin.

7. Use of an anthracycline of formula Ia or Ib as defined in claim 1 and an anti-neoplastic anti-mitotic compound and/or a platinum derivative in the preparation of a medicament for use in the treatment of tumors.

8. Use according to claim 7 wherein the anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin.

9. Use of a product as defined in claim 1 in the preparation of a medicament for use in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis.